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CP-96345 Rregulates Hydrogen Sulphide Induced TLR4 Signaling Pathway Adhesion Molecules in Caerulein Treated Pancreatic Acinar Cells

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Abstract : We have earlier shown that mouse pancreatic acinar cells produce hydrogen sulfide (H2S) and play a role in the pathogenesis of acute pancreatitis. This study is to determine the effect of H2S on TLR4 mediated innate immune signaling in acute pancreatitis via substance P (SP). Male Swiss mice were treated with hourly intraperitoneal injection of caerulein (50µg/kg) for 10 hour. DL-propargylglycine (PAG) (100 mg/kg i.p.), an inhibitor of H2S formation was administered 1h after the induction of acute pancreatitis. Pancreatic acinar cells from male Swiss mice were incubated with or without caerulein (10–7 M for 60 min) and CP-96345 (NK1R inhibitor). To better understand the effect of H2S in inflammation, acinar cells were stimulated with caerulein after addition of H2S donor, NaHS. In addition, caerulein treated pancreatic acinar cells were pretreated with PAG (30 µM), for 1h. H2S inhibitor, PAG, eliminated TLR4, IRAK4, TRAF6 and NF-kB levels in an in vitro and in vivo model of caerulein-induced acute pancreatitis. PPTA gene deletion reduced TLR4, MyD88, IRAK4, TRAF6, adhesion molecules and NF-kB in caerulein treated pancreatic acinar cells whereas administration of NaHS resulted in further rise in TLR4 and NF-kB levels in caerulein treated pancreatic acinar cells. In addition, acini isolated from mice and treated with PPTA gene receptor NK1R antagonist CP96345 did not exhibit further increase in TLR4, IRAK4, TRAF6, adhesion molecules and NF-kB levels after NaHS pretreatment. The present findings show for the first time that in acute pancreatitis, H2S up-regulates TLR4 pathway and NF-kB via substance P.

Keywords : preprotachykinin-A gene, H2S, TLR4, acute pancreatitis
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